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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

March 20, 1981

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Advisory Opinion on the Oncogenic Potential
of Permethrin

FROM: Philip H. Gray, Jr. *Phil Gray*
Acting Executive Secretary
FIFRA Scientific Advisory Panel (TS-766)

TO: Deputy Assistant Administrator
for Pesticide Programs (TS-766)

The FIFRA Scientific Advisory Panel convened in a special meeting on March 10, 1981, to respond to certain questions posed by the Office of Pesticide Programs/Hazard Evaluation Division regarding the oncogenic potential of Permethrin. The Panel completed its assigned task in an open meeting held in Arlington, Virginia on that same day.

Present at the meeting were the following Panel members: Dr. Dewayne Torgeson, Chairman; Dr. John Davies; Dr. John Doull; and Dr. Edward Smuckler. Also present as an ad hoc Panel member was Dr. Robert Tarone, a biostatistician from the National Cancer Institute.

Attached is a report of findings by the Panel.

Attachment
Report

cc: Mr. Conlon
Dr. McGrath
Mr. Campt
Mary Beatty
Charles Smith
✓ Mr. Burnam

FEDERAL INSECTICIDE, FUNGICIDE, AND RODENTICIDE ACT (FIFRA)

SCIENTIFIC ADVISORY PANEL

ADVISORY OPINION ON THE ONCOGENIC POTENTIAL OF PERMETHRIN

In response to a request by the Agency, the FIFRA Scientific Advisory Panel convened a special meeting to address the oncogenic potential of Permethrin. The Panel completed this assigned task in an open meeting held in Arlington, Virginia on March 10, 1981. The meeting was announced in the Federal Register on February 24, 1981.

Written and oral statements were received from technical staff and representatives of the Environmental Protection Agency; from representatives of ICI Americas and FMC Corporation; and from representatives of Burroughs-Wellcome Company.

STATEMENT OF ISSUES AND DISCUSSION TOPICS

The Agency requested the Panel to consider the following issues: with respect to the FMC/ICI and Burroughs-Wellcome studies in mice, the Panel was requested to provide its views and conclusions on:

- The relative usefulness of each of these studies in evaluating the oncogenic potential of Permethrin.
- Pathological findings in the FMC Mouse II Study.
- The use of historical control data in the evaluation of the FMC Mouse II Study.
- The overall evidence and likelihood for oncogenicity provided by the totality of the studies and particularly the FMC Mouse II and Burroughs-Wellcome Mouse studies.
- The apparent oncogenic potency of Permethrin.
- Which of the data bases are most useful and important for purposes of developing a dose-response curve.

PANEL REPORT

With respect to each of the issues mentioned above, the Panel submitted the following report:

1. The relative usefulness of each of these studies in evaluating the oncogenic potential of Permethrin.

According to the Panel, long-term feeding studies are, at present, the only avenue for detection of cancer production in animals. These are not perfect experiments, but the better the laboratory practice, the more critical the pathological, anatomical and clinical survey, the more secure the data that is produced. For these reasons the relative "usefulness" of the seven studies must be considered in context.

- a) The ICI of Burroughs-Welcome and FMC rat studies all fail to show any modification in incidence of proliferative lesions following feeding with permethrin. There are positive responses to feeding in these animals (e.g., increased liver weight, mixed function oxidase induction) that point to a pharmacological effect, hence revealing a positive built-in assay of chemical effect. This lends credence to the negative aspect of the carcinogenesis assays.
- b) The mouse studies are clouded. The ICI and Burroughs-Welcome studies appear well controlled and properly carried out. The latter reveals a potential pulmonary neoplasm production. The FMC studies I and II are clouded by controversy concerning their execution (dosing, animal identification, gross and microscopic examination) that they are rendered uninterpretable. They suggest but do not show a potential for the production of pulmonary and hepatic proliferative lesions, an unease, not a definitive demonstration.

In summary, the Panel recommended that EPA rely more upon the rat studies than upon the mouse studies in reaching regulatory decisions regarding Permethrin.

2. Pathological findings in the FMC Mouse II Study.

The Panel expressed a marked lack of confidence in the pathological findings of the FMC Mouse II Study. The confusion concerning the execution of the study, the problems of potential intercurrent disease, no clear indication of tissue examination by the pathologist during gross examination, and the selection of tissue for histology make this data uninterpretable.

3. The use of historical control data in the evaluation of the FMC Mouse II Study.

According to the Panel, historical controls provide an assay of the status of the circumstances surrounding an experiment. Inbred animals treated under identical conditions should show reproducible indices

of naturally occurring disease. This is an assay of the "standard conditions." These data should be accompanied by age data at the time of examination and survival data. The FMC Mouse II study had already been compromised by its execution. The historical data only added to uncertainty concerning mouse responsiveness. Thus, such data should not be used on an ad hoc basis simply in an effort to provide answers in the case of a study of questionable validity, but rather should be used as a matter of course in reviewing all scientific studies on pesticide effects.

4. The overall evidence and likelihood for oncogenicity provided by the totality of the studies and particularly the FMC Mouse II and Burroughs-Wellcome Mouse Studies. (See below #5)
5. The apparent oncogenic potency of Permethrin.

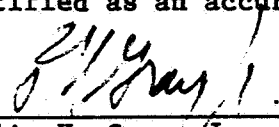
The ICI and FMC Mouse II studies suggest that there may be a very small possibility of carcinogenic potential of Permethrin in mice. Coupled with the rat studies, this suggests a very limited potential and/or potency, or none at all. The Panel thus expressed the view that, based on all the data together, the oncogenic potential of Permethrin was very weak. The possibility of oncogenic potential in man was extremely remote.

6. Which of the data bases are most useful and important for purposes of developing a dose-response curve.

The Panel stated that it was difficult to establish a dose response curve based on the current data, inasmuch as none of the available studies provide for such a curve. Mouse liver and lung tumors are extremely variable in natural incidence; assay for carcinogenesis with these as targets seem a particularly poor prediction and especially so for man, according to the Panel.

FOR THE CHAIRMAN:

Certified as an accurate Report of Findings:



Philip H. Gray, Jr.
Acting Executive Secretary
FIFRA Scientific Advisory Panel

DATE: March 20, 1981